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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,189	09/21/2006	Alexei Shir	29770	5260

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
11/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,189	SHIR ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008 and 22 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-109* is/are pending in the application.

4a) Of the above claim(s) *72-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed April 28, 2008 and Applicant's Election filed August 22, 2008.

Claim 96 has been amended. New claims 99-106 are acknowledged.

Claims 72-109 are pending in the instant application.

This application contains claims 72-95 drawn to an invention nonelected without traverse in the reply filed on October 11, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election of Species

Applicant's election of Species IV, biocompatible polymer from claim 108 in the reply filed on August 22, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 96-109 have been examined on the merits.

Specification

In the previous Office Action mailed, December 27, 2007, the specification was objected to because the specification at pages 21, 27, and 47 contained embedded hyperlinks and/or other forms of browser-executable code that are impermissible and must be deleted. **This objection is withdrawn** in view of Applicant's Amendment to the Specification filed April 28, 2008 to remove embedded hyperlinks and/or other forms of browser-executable code.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed, December 27, 2007, claims 96-98 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicant's Amendment to the claims filed April 28, 2008. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to claim 96 to correct for grammar.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed, December 27, 2007, claims 96-98 were rejected under 35 U.S.C. 102(a) as being anticipated by Abounader et al. (The FASEB Journal, 2002 Jan;16(1):108-10. Epub 2001 Nov 29). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed December 27, 2007.

Response to Arguments

In response to this rejection, Applicants argue that the claims have been amended such that the association of the targeting moiety is limited to the nucleic acid carrier and not the RNA molecule itself. In view of this Amendment, Applicants contend that the ribozymes disclosed by Abounader et al. selectively relies on down-regulation of RNA molecules which are specifically expressed in target cells, where cells which do not express the RNA molecule which is specifically targeted by the ribozymes will therefore not be affected. Applicants argue that the compositions for cell killing of the present invention rely on double stranded RNA which is cytotoxic to **all** cells. In contrast, Applicants argue that the cell killing of Abounader et al. is brought about by the use of specific targeting moieties on carrier molecules comprising the double stranded RNA.

Applicant's arguments and contentions have been fully considered, but are not found persuasive. The Examiner acknowledges that the instant claims are drawn to:

A method of killing a specific target cell and/or tissue, the method comprising exposing the specific target cell and/or tissue to a composition-of-matter comprising
(i) a double stranded RNA molecule;
(ii) a nucleic acid carrier; and
(iii) a targeting moiety,
said double stranded RNA molecule being associated with said nucleic acid carrier, said carrier being associated with said targeting moiety and said targeting moiety is for targeting to the specific target cell and/or tissue, thereby killing the specific target cell and/or tissue.

Now then, Abounader et al. disclose a method of increasing programmed cell death and apoptosis in specific cells, the method comprising administering a double stranded RNA molecule (see double-stranded nucleic acid sequences of the ribozyme in Figure 1A); a nucleic acid carrier (see vector used for *in vivo* delivery); and a targeting

moiety (see two complementary pairs of AS/ribozyme sequence, chosen to cleave the targeted mRNA in Figure 1A and page 2). It is noted that the double stranded RNA molecule is associated with the nucleic acid carrier by ligation/annealing and the nucleic acid carrier is associated with the targeting moiety by ligation/annealing. It is further noted that Applicants have not defined the term "targeting moiety". Applicant is reminded that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. Given its broadest reasonable interpretation, the Examiner has interpreted the term "targeting moiety" to consist of the two complementary pairs of ribozyme sequences, chosen to cleave the targeted mRNA, where those cells expressing the target are selectively killed.

Therefore, Abounader et al. anticipate claims 96-98.

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In the previous Office Action mailed, December 27, 2007, claims 96-98 were rejected under 35 U.S.C. 102(b) as being anticipated by Czubayko et al. (Proc. Natl. Acad. Sci., 1996 Vol. 93:14753-14758). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed December 27, 2007.

Response to Arguments

In response to this rejection, Applicants argue that the claims have been amended such that the association of the targeting moiety is limited to the nucleic acid

carrier and not the RNA molecule itself. In view of this Amendment, Applicants contend that the ribozymes disclosed by Czubayko et al. selectively relies on down-regulation of RNA molecules which are specifically expressed in target cells, where cells which do not express the RNA molecule which is specifically targeted by the ribozymes will therefore not be affected. Applicants argue that the compositions for cell killing of the present invention rely on double stranded RNA which is cytotoxic to **all** cells. In contrast, Applicants argue that the cell killing of Czubayko et al. is brought about by the use of specific targeting moieties on carrier molecules comprising the double stranded RNA.

Applicant's arguments and contentions have been fully considered, but are not found persuasive because Czubayko et al. disclose a method of increasing programmed cell death and apoptosis in specific cells, the method comprising administering a double stranded RNA molecule (see double-stranded "catalytic center" of the ribozyme used at page 14754, first column); a nucleic acid carrier (see vector used for *in vivo* delivery); and a targeting moiety (antisense flanking regions that target the ribozyme transcripts to their cleavage site at page 14754, first column). It is noted that the double stranded RNA molecule is associated with the nucleic acid carrier by ligation/annealing and the nucleic acid carrier is associated with the targeting moiety by ligation/annealing. As discussed *supra*, Applicants have not defined the term "targeting moiety" and therefore, the Examiner has interpreted the term "targeting moiety" broadly to include the antisense flanking regions that target the ribozyme transcripts to their cleavage site, where those cells expressing the target are selectively killed.

Therefore, Czubayko et al. anticipate claims 96-98.

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In the previous Office Action mailed, December 27, 2007, claims 96-98 were rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (Development, 1998 Vol. 125:1899-1907). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed December 27, 2007.

Response to Arguments

In response to this rejection, and as discussed *supra*, Applicants argue that the claims have been amended such that the association of the targeting moiety is limited to the nucleic acid carrier and not the RNA molecule itself. In view of this Amendment, Applicants contend that the ribozymes disclosed by Zhao et al. selectively relies on down-regulation of RNA molecules which are specifically expressed in target cells, where cells which do not express the RNA molecule which is specifically targeted by the ribozymes will therefore not be affected. Applicants argue that the compositions for cell killing of the present invention rely on double stranded RNA which is cytotoxic to **all** cells. In contrast, Applicants argue that the cell killing of Zhao et al. is brought about by the use of specific targeting moieties on carrier molecules comprising the double stranded RNA.

Applicant's arguments and contentions have been fully considered, but are not found persuasive because Zhao et al. disclose a method selectively killing retinal cells,

the method comprising administering a double stranded RNA molecule (see double-stranded nucleic acid sequences of the ribozyme in Figure 1); a nucleic acid carrier (see vector used for delivery); and a targeting moiety (flanking nucleotides that base pair with target NRG-1 sequence in Figure 1). It is noted that the double stranded RNA molecule is associated with the nucleic acid carrier by ligation/annealing and the nucleic acid carrier is associated with the targeting moiety by ligation/annealing. As discussed *supra*, Applicants have not defined the term "targeting moiety" and therefore, the Examiner has interpreted the term "targeting moiety" broadly to include the flanking nucleotides that base pair with target NRG-1 sequence, where those cells expressing the target are selectively killed.

Therefore, Zhao et al. anticipate claims 96-98.

Applicant's Amendment filed April 28, 2008 necessitated the new grounds of rejection presented below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 96-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/23050 (submitted on Applicant's Information Disclosure Statement filed February 7, 2007) in view of Yamazaki et al. (Journal of the National Cancer Institute, 1998 Vol. 90:581-587) and Ogris et al. (Journal of Biological Chemistry, 2001 Vol. 276:47550-47555).

Claim 96 is drawn to a method of killing a specific target cell and/or tissue, the method comprising exposing the specific target cell and/or tissue to a composition-of-matter comprising (i) a double stranded RNA molecule; (ii) a nucleic acid carrier; and (iii) a targeting moiety, said double stranded RNA molecule being associated with said nucleic acid carrier, said carrier being associated with said targeting moiety and said targeting moiety is for targeting to the specific target cell and/or tissue, thereby killing the specific target cell and/or tissue. Claims 97-109 are dependent on claim 96 and includes all the limitations of claim 96 with the further limitations wherein said exposing

the specific target cell and/or tissue to said composition-of-matter is effected by administering said composition-of-matter to a vertebrate subject bearing the specific target cell and/or tissue; wherein said administering said composition-of-matter to said vertebrate subject is effected by administering said composition-of-matter to said subject systemically and/or to a central nervous system location of said vertebrate subject; wherein said composition-of-matter further comprises melittin; wherein said targeting moiety is a ligand of a surface marker of said specific cell and/or tissue; wherein said ligand of said surface marker is a biological ligand of said surface marker; wherein said targeting moiety is an antibody or antibody fragment; wherein said targeting moiety is a growth factor; wherein said growth factor is epidermal growth factor; wherein said surface marker is a growth factor receptor; wherein said surface marker is epidermal growth factor receptor; wherein said double stranded RNA comprises a polyinosinic acid stand and/or a polycytidylic acid strand; wherein said nucleic acid carrier comprises a biocompatible polymer; and wherein said polymer is PEI or PEG.

Determining the scope and contents of the prior art

WO 94/23050 teaches and claims a method of blocking translation of an RNA transcript in a cell or an organism, comprising administering to an organism a soluble molecular complex comrpisng an expressible gene encoding an RNA which hybridizes to and inhibits the function of a cellular RNA, the RNA being complexed with a carrier comprising a cell-specific binding agent and a gene-binding agent (see Abstract and claim 20). WO 94/23050 teaches the cell-specific binding agent is specific for a cellular

surface structure which mediates internalization of ligands by endocytosis and the gene-binding agent is a compound such as a polycation which stably complexes the gene under extracellular conditions and releases the gene under intracellular conditions so that it can function within a cell. WO 94/23050 also teaches that the binding agent is an antibody (see page 3, lines 21 and 22). WO 94/23050 teaches that the molecular complex is stable and soluble in physiological fluids and can be used in antisense gene therapy to selectively transfect cells *in vivo* (see Abstract). WO 94/23050 also teaches and claims that the antisense RNA is a ribozyme (see claim 28).

Yamazaki et al. teach a method of inhibiting cellular growth and killing tumor cells, the method comprising administering a double stranded RNA molecule (see double-stranded nucleic acid sequences of the ribozyme in Figure 1); a nucleic acid carrier (see vector used for *in vivo* delivery); and a targeting moiety (regions of complementary sequence in Figure 1). It is noted that the double stranded RNA molecule is associated with the nucleic acid carrier by ligation/annealing and the nucleic acid carrier is associated with the targeting moiety by ligation/annealing. It is further noted that Applicants have not defined the term "targeting moiety". Applicant is reminded that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. Given its broadest reasonable interpretation, the Examiner has interpreted the term "targeting moiety" to include the regions of complementary sequence in Figure 1, where those tumor cells expressing the target are selectively killed.

Yamazaki et al. also teach that the dsRNA ribozyme is a epidermal growth factor receptor (EGFR) that targets aberrant EGFR substrates and transcripts (see Abstract).

Ascertaining the differences between the prior art and the claims at issue

Neither WO 94/23050 nor Yamazaki et al. teach wherein the composition-of-matter further comprises melittin or wherein the nucleic acid carrier comprises a biocompatible polymer, including PEI or PEG.

Ogris et al. teach that melittin, a cationic membrane-active short peptide enables efficient vesicular assess of gene delivery vectors (see Abstract). Specifically, Ogris et al. teach that melittin-PEI•DNA complexes exhibit higher transfection efficiency than PEI/DNA complexes alone (see Figures).

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to devise a method of killing a specific target cell and/or tissue, the method comprising exposing the specific target cell and/or tissue to a composition-of-matter comprising (i) a double stranded RNA molecule; (ii) a nucleic acid carrier; and (iii) a targeting moiety, said double stranded RNA molecule being associated with said nucleic acid carrier, said carrier being associated with said targeting moiety and said targeting moiety is for targeting to the specific target cell and/or tissue, thereby killing the specific target cell and/or tissue using the teachings of

WO 94/23050 and Yamazaki et al. It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to have the composition-of-matter further comprises melittin using the teachings of Ogris et al. It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to have the nucleic acid carrier comprise PEI using the teachings of Ogris et al.

One of ordinary skill in the art would have been motivated to devise a method of killing a specific target cell and/or tissue, the method comprising exposing the specific target cell and/or tissue to a composition-of-matter comprising (i) a double stranded RNA molecule; (ii) a nucleic acid carrier; and (iii) a targeting moiety, said double stranded RNA molecule being associated with said nucleic acid carrier, said carrier being associated with said targeting moiety and said targeting moiety is for targeting to the specific target cell and/or tissue, thereby killing the specific target cell and/or tissue because WO 94/23050 and Yamazaki et al. taught such a method could inhibit the growth of tumors *in vivo*. One of ordinary skill in the art would have been motivated to have the composition-of-matter further comprise melittin and to have the nucleic acid carrier comprise PEI because Ogris et al. taught that melittin-PEI•DNA complexes are great candidates for systemic gene delivery *in vivo*.

One of ordinary skill in the art would have had a reasonable expectation of success of devising a method of killing a specific target cell and/or tissue, the method comprising exposing the specific target cell and/or tissue to a composition-of-matter comprising (i) a double stranded RNA molecule; (ii) a nucleic acid carrier; and (iii) a targeting moiety, said double stranded RNA molecule being associated with said nucleic

acid carrier, said carrier being associated with said targeting moiety and said targeting moiety is for targeting to the specific target cell and/or tissue, thereby killing the specific target cell and/or tissue since Yamazaki et al. taught the successful use and design of such a method to inhibit tumor growth in mice. One of ordinary skill in the art would have had a reasonable expectation of success of having the composition-of-matter further comprises melittin since Ogris et al. taught the successful use and delivery of melittin and DNA complexes to a whole animal. One of ordinary skill in the art would have had a reasonable expectation of success of having the nucleic acid carrier comprise PEI since Ogris et al. taught the successful use and delivery of melittin-PEI•DNA complexes *in vivo*.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

November 20, 2008
/Terra Cotta Gibbs/

/Sean R McGarry/

Primary Examiner, Art Unit 1635